THE PATHOLOGY OF HEREDITARY CHOREA. REPORT OF A CASE WITH AUTOPSY. RECORD OF ANOMALIES IN A DEGENERATE BRAIN.

By CHARLES L. DANA, M.D.

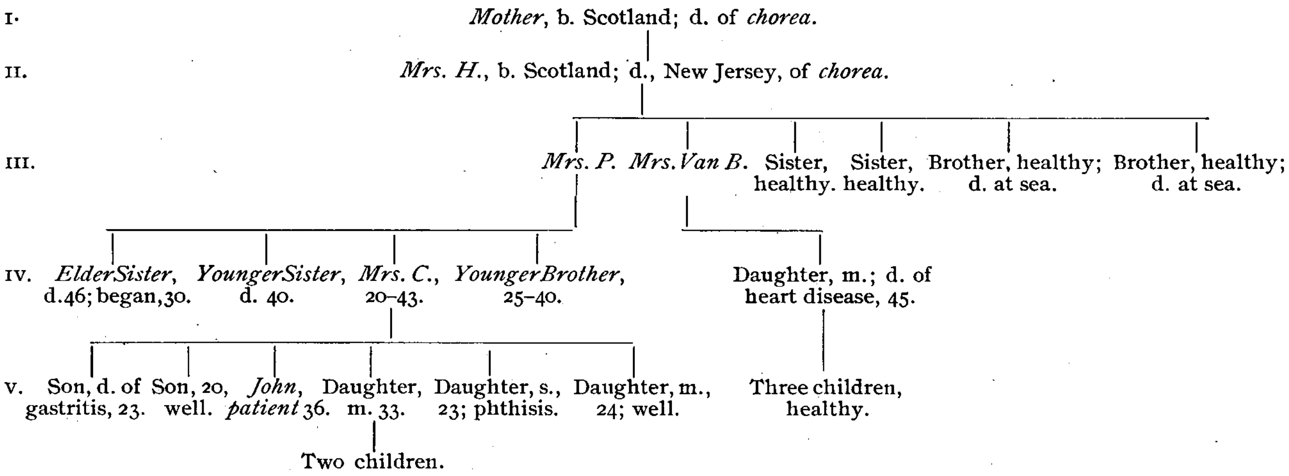
THE clinical history of ereditary or Huntington's chorea is very thoroughly known, and I should not feel justified in reporting a case on the ground of its symptological features alone. In the present instance, however, the patient died somewhat early in the disease, from typhoid fever, and I was able to make an examination of the brain before the malady had advanced to its last stage. The patient had also a most remarkable hereditary history.

CLINICAL HISTORY.—John C. was thirty-seven years old at the time of his death. He was single, born in New Jersey, and was sent to my clinic at the Post-Graduate School in 1892 by Dr. George R. Elliott, to whom I am greatly indebted for notes in the case and for assistance in preparing the pathological specimens.

The hereditary history of the patient is extremely interesting and almost unique in the extent and definiteness of the hereditary transmission. Through correspondence and personal interviews I have been able to trace back his disease into the fifth generation. The accompanying table will show better than any elaborate description exactly how the disease has been transmitted.

The original sufferer was a great great-grandmother, who was born in Scotland and who died, as tradition gives it in the family, of chorea. The great-grandmother was also born in Scotland and died in New Jersey of choreic dementia. The grandmother also died of a chorea which began after the age of thirty. The mother of the present patient also died of chronic chorea, which developed after the age of thirty. She died at the age of forty. The patient himself began to develop choreic

GENEALOGY OF A CASE OF HEREDITARY CHOREA.*


I. *Mother*, b. Scotland; d. of *chorea*.
II. *Mrs. H.*, b. Scotland; d., New Jersey, of *chorea*.
III. *Mrs. P.*
Mrs. Van B.
Sister, healthy.
Sister, healthy.
Brother, healthy; d. at sea.
Brother, healthy; d. at sea.
IV. *ElderSister*, d.46; began,30.
YoungerSister, d. 40.
Mrs. C., 20–43.
YoungerBrother, 25–40.
Daughter, m.; d. of heart disease, 45.
V. Son, d. of gastritis, 23.
Son, 20, well.
John, *patient* 36.
Daughter, m. 33.
Daughter, s., 23; phthisis.
Daughter, m., 24; well.
Three children, healthy.
Two children.

* The persons in italics were those who had chorea.

symptoms at the age of about thirty-three and died at the age of thirty-seven from typhoid fever, having reached about the middle stage apparently of his disease, for, judging from the course of it in his ancestors, the malady lasted ten or twelve years. The family history shows also hereditary chorea in a great aunt, and in the aunts and uncles of the present patient. None of the brothers and sisters had yet begun to suffer from the affection, but the patient was the oldest, and it still remains to be seen whether the disease will be developed in the other members of the last generation.

The genealogical record shows that the disease is transmitted entirely through the female members of the family, but that all the female members of the family did not transmit it, even though some of them had the disease themselves. It also shows that the disease developed with almost absolute definiteness in time at the age of thirty-two or thirty-three years. So far as the accounts go, the symptoms seem to have been pretty nearly the same, the patients developing at first choreic movements of marked type, and then mental symptoms which ended in chronic mania and dementia. The disease was in the earliest manifestations more of the nature of the ordinary chorea, but, as it became transmitted from generation to generation, the motor element became less marked and the symptoms of a progressive dementia were the most prominent.

The disease began in my patient with no exciting cause, and the first symptoms were a slight disturbance in articulation. This was accompanied with twitching of the lips and choreic movements of the facial muscles. As the disease advanced, twitching movements of the head and of the arms became noticeable. The gait was of the peculiar loping or high-stepping character. A short time after the development of the speech troubles the patient showed some disturbance of the mind. He became easily excited, and sometimes was violently angry over slight things. His memory failed, and he was unable to perform the ordinary duties of his work, which was that of a pedlar. His father finally consented to his admission to the hospital, as he was of no help at home, and his temper was becoming a somewhat disturbing element in the family.

A physical examination of the patient on admission showed him to be a strongly built, muscular man of about 5 feet 7 in. in height. His gait was characteristic of

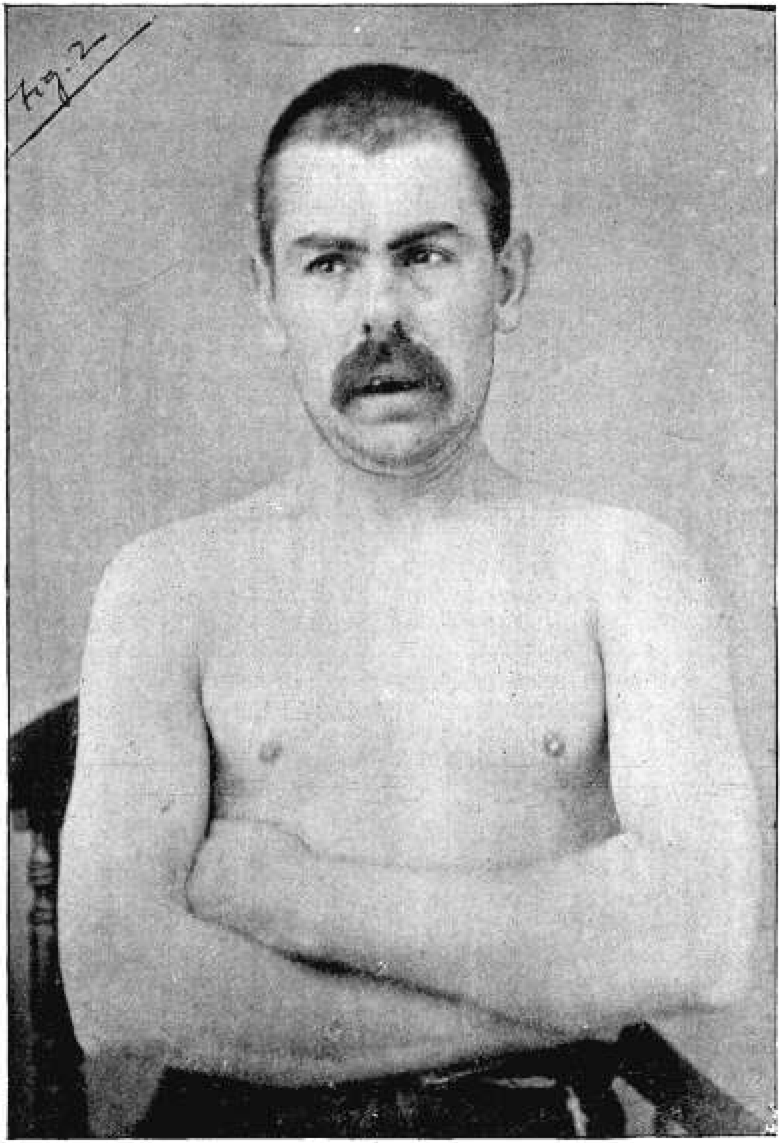


FIG. 1. Physiognomy of patient in fifth year of the disease.

the hereditary chorea, that is to say, his steps were long and high, and his body swayed to and fro in walking; his head at the same time made a nodding motion so that his appearance was very striking. He showed some twitching movements in the facial muscles and occasionally in the shoulders and arms. The tongue protruded with some difficulty, and he did not seem to have full control of it. There was no nystagmus, but the eye muscles would twitch at times. He had no paralysies or atrophies, no pains, or anæsthesias, and no trophic disturbances of the skin. He could stand with the eyes closed and showed in no way any evidence of ataxia; the knee-jerks were normal. His bodily organs —lungs, heart, kidneys and digestive tract were all healthy. His mind was in a weakened state; his memory was defective; he was slow in comprehension, irritable in temper and flew out in the most violent rage at times. He was, however, not yet in any great degree silly or demented, and was able to answer questions quite intelligently. He was fond of being left alone and would sit in his chair reading Shakespeare's plays or Gibbon's History of Rome, apparently enjoying them. Later he took to newspapers and betrayed his intellectual decay by giving up the classics for the daily news.

He continued in the hospital most of the time up to July, 1894, a period of about two years. During this period his motor symptoms did not change very much. He still had the peculiar high-stepping gait, nodding movements of the head, the choreic twitchings of the face, the peculiarities of speech. His temper became somewhat milder and he himself became rather weaker in mind, though still able to do ordinary work about the wards.

In January, 1893, I made a trephine opening over the motor centre for the head, neck and eyes on the right side of the brain. This was done with the consent of his father and himself, and the operation was performed in the hope that by some mechanical interference of this sort the natural progressive tendency of the disease might be checked, as had been reported to be the case in general paresis. As a matter of fact this result did follow, and for five or six months after the operation he was decidedly brighter and better. He then gradually relapsed into his former state. In June, 1894, he develloped typhoid fever, the fever running from June 17th to July 13th, when he died. The symptoms during this

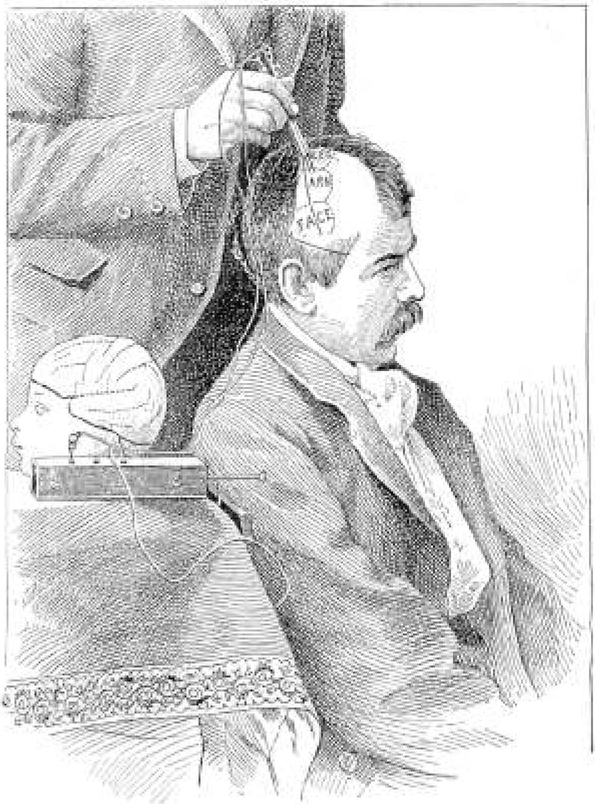


FIG. 2. Showing location of trephine opening.

time were those of a somewhat severe type. The duration of the high temperature was from July 3 to 14, about eleven days, so that he may be said to have died in the second week of the disease. Death was caused by intestinal perforation and septic peritonitis.

THE POST-MORTEM was made by my house physician, Dr. Pearce, to whom I am indebted for the notes, and I have also to express my indebtedness to my colleague, Dr. Alexander Lambert, through whose courtesy I was able to obtain the specimens.

The autopsy showed the usual changes in the intestines that characterize typhoid. There was a distinct point of perforation in the ileum. The kidneys were small with numerous cystic tumors over the surface, but not otherwise diseased. There were nothing abnormal about the lungs, liver or spleen, except such changes as were due to the fever. The heart was small; the wall of the right ventricle thin; the heart muscle pale; the valves were normal and there was no encarditis.

On removing the calvarium the dura mater was found to be thickened and adherent to the bone along the longitudinal fissure, and also firmly adherent at the seat of the trephine. It was not, however, adherent to the arachnoid beneath, nor was there much thickening of the pia-arachnoid. The brain itself was congested, but showed no other marked changes to the naked eye, the vessels not appearing diseased. There was not any great amount of œdema. The brain and spinal cord were placed in Müller's fluid, hardened and then subjected to examination by various methods, with Weigert's stain, carminate of soda, logwood, and methyl blue. Owing to my absence at the time of the patient's death it was not possible to make any stains by the method of Nissl or that of Lewis.

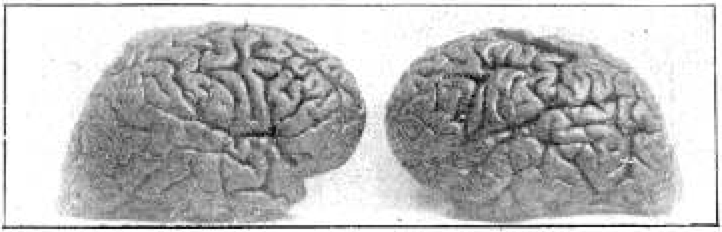
ANATOMICAL ANOMALIES OF THE BRAIN.—The study of the present case from its pathological aspect presents two features of striking interest. One of them is that of the gross character of the brain as compared with normal brains; the other, that of the microscopic findings and the minute changes underlying the course of the disease. It seemed to me that a brain belonging to a family having such a striking history of transmitted degeneration might, perhaps, present some peculiar characters. Here was a man whose ancestors for four generations had with the persistence and certainty of a machine begun to go through precisely the same disease changes soon after the age of thirty, although apparently sound and vigorous men and women before that. There was evidently at their birth some potentiality for early degeneration. Whether the brain itself showed on the surface characters which would indicate that it was an organ that would be liable to early deterioration was a question which I sought to answer.

I first of all made some examination of the head and skull. This gave, however, rather few of the stigmata of degeneration. As the picture shows (Fig. 1), the face is not that of a very intelligent man, but the head is normal in size (g c = 54.) and symmetrical. The patient had coarse hair, thick bushy eyebrows, badly set teeth, a high, narrow, arched palate, and a slight amount of facial asymmetry. He was a man of strong muscular development. The brain was carefully photographed after it had been hardened in Müller's fluid for three months, and the pia mater removed. I made some careful studies then of the arrangement of the convolutions, taking measurements of the different parts. I also made a series of one hundred and fifty measurements of the thickness of the different parts of the cortex. The results of these studies I append here.

THE FISSURAL ARRANGEMENT.

1. The Fissure of Rolando.

Left.—The fissure measures 12 ctm. in its total length measured with a moist thread. Above it does not quite reach the longitudinal fissure. At the lower third it is interrupted by a bridging convolution and the lowest third runs into the fissure of Sylvius.



a. *b.*

FIG. 3. Brain of hereditary chorea. *b*, left hemisphere, interrupted fissure Rolando.

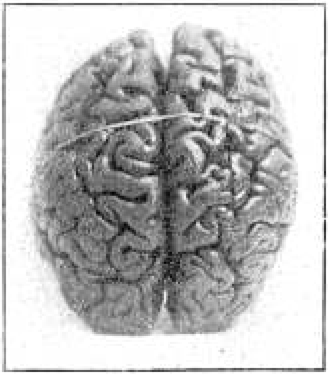


FIG. 4. Showing absence of *pli de passage* on right side.

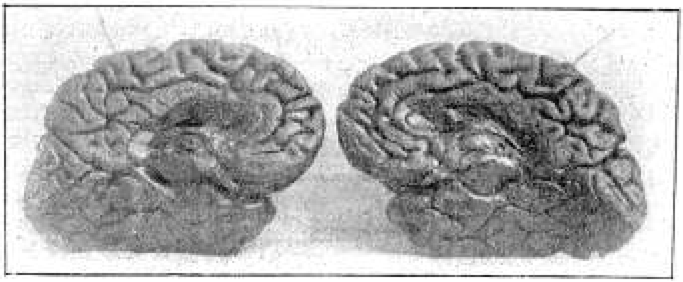


FIG. 5.

Right.—The fissure above runs over into the longitudinal fissure. It is 12½ ctm. long and forms a normal angle with the longitudinal fissure. It presents no special peculiarities.

2. *The Fissure of Sylvius.*

Left.—The posterior branch is quite long, measuring 7 ctm. and ends in a fissure running at right angles to its course which is confluent with the first temporal below. The fissure is itself confluent with the fissure of Rolando. Vertical branch is very long, measuring 4.2 ctm. The fossa is covered; the anterior branch is of average length.

Right.—The fissure of Sylvius is long and straight. The posterior branch measuring 8 ctm. The retro-centre fissure runs into it. The anterior and vertical portions are very long, the frontal branch measuring 4 ctm.; the vertical 3.7.

3. The Parietal Fissure

Left.—The superior part of the retro-centre fissure is irregular in course and runs into the fissure of Rolando. The inferior part is continuous with the middle part of the parietal, and the middle part of the parietal is entirely independent of the occipital.

On the *right* hemisphere the superior and inferior parts of the retro-central fissure unite and form one continuous fissure parallel to the fissure of Rolando. The parietal part is connected with this, but is entirely disconnected with the occipital. This entire separation of the parietal part from the occipital portion on both sides is the only peculiarity of the fissure. I have seen it occur in a low type negress' brain, but I cannot say that it might not be found in normal brains.

4. The Occipital fissure, left side, is well marked and presents nothing abnormal. The external branch measures 1.8 ctm. in length. On the right side the occipital fissure is deep, very well marked and runs into the paroccipital of Wilder, so that there is no superior external *pli de passage*. This latter is the only peculiarity that I note in connection with the occipital fissures. The anterior occipital fissure of Wernecke is well marked in both right and left hemisphere. The anterior occipital as described by Eberstaller is very poorly marked.

The first temporal on the left side is short, runs into the fissure of Sylvius and also into the second temporal, and does not run into the anterior occipital of Wernecke. On the right side the first temporal is broken in two parts, the second being confluent with the second temporal.

The third temporal is broken in two parts on the left side and in three parts on the right.

The fourth temporal is a continuous fissure ending in a T fissure. In the right hemisphere from the under surface of the occipital lobe is a transverse fissure, making the head of a T with the fourth temporal fissure and running from the junction of the occipital and calcarine fissure to the external border of the occipital lobe.

The inferior præ-central fissure is normal and confluent with the second frontal fissure. The superior part of the præ-central fissure is also well marked and continuous, not confluent. The medi-central fissure is distinct and not confluent, the frontal convolutions have, therefore, a rather simple type. All this applies to the left hemisphere. On the right side the inferior præ-central is long and runs into the second frontal fissure, which is short with many transverse fissures. The superior part of the præ-central is distinct and continuous, and so also is the medi-frontal fissure, which is not connected with either the first or second frontal.

The calloso-marginal fissure on the right side is continuous. On the right side also continuous and not confluent upon either side.

SUMMARY OF ANOMALIES. In reviewing these observations upon the arrangement of the fissures, I note a few peculiarities which may be considered of significance. These are the interruption in the fissure of Rolando by a bridging convolution. This anomaly is certainly rare, and probably has some significance as an evidence of imperfect evolution of the brain. The arrangement of the retro central fissure so that it parallels without any interruption the fissure of Rolando, and runs into the fissure of Sylvius is perhaps of some significance also. The confluence of the occipital fissure with the par-occipital, thus cutting off the *pli de passage* is a decided anomaly. The simple arrangement of the frontal convolutions with the fissures well divided and not confluent, and the peculiarities of the anterior occipital of Wernicke and of the fourth temporal indicated in the description above, complete the list of what may be called anomalies. Taken as a whole, it will be seen that the brain carries in its configuration two or three striking evidences of its being an peculiarly developed organ.

I append now some measurements of the different parts of the brain which may be of use for comparison in other studies.

MEASUREMENTS IN CENTIMETRES.

Weight, 49 oz.

	Right.	Normal average.	Left.
Trigonum to occipital pole	34.	33.6	33.5
" " fissure	28.	28.	
" fissure Rolando	21.5	22.	22.5
Total length of brain	17.5	16.2 to 17.2	
" " corpus callosum	7.1		
Occipital fissure to occipital pole	6.		5.
Fissure of Rolando,			
Sinuous length	12.5	11.3	12.
Straight "	11.		
Fissure Sylvius,			
Posterior branch	8.	7.28	7.
Fossa	2.5		2.
Frontal branch	4.		
Vertical "	3.7		4.2
Occipital Fissure external branch	2.		1.8
Central Convolutions,			
Breadth of both lower parts	3.		
Præ-central, average of 10 measurements	1.		
do. of post central	1.2		

THE RELATIVE CORTICAL THICKNESS.—A good deal may be learned regarding the condition and development, or lack of development, of the brain by studying the thickness of the gray matter in the different areas. I pursued this plan with the brain of a Peruvian Indian, and I have examined other brains in similar

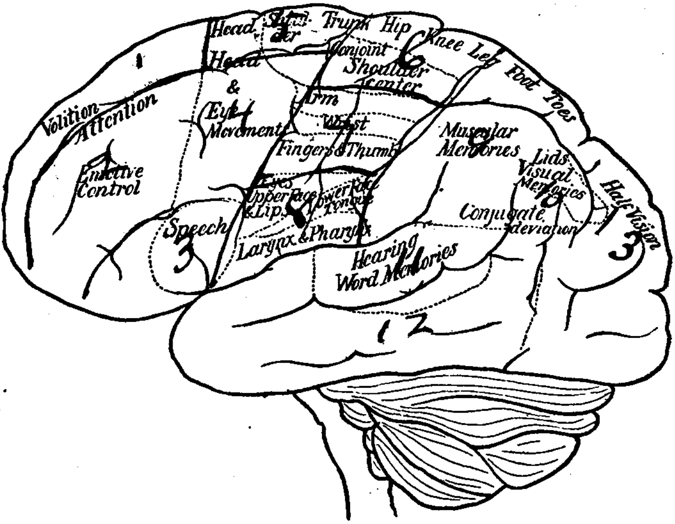


FIG. 6.

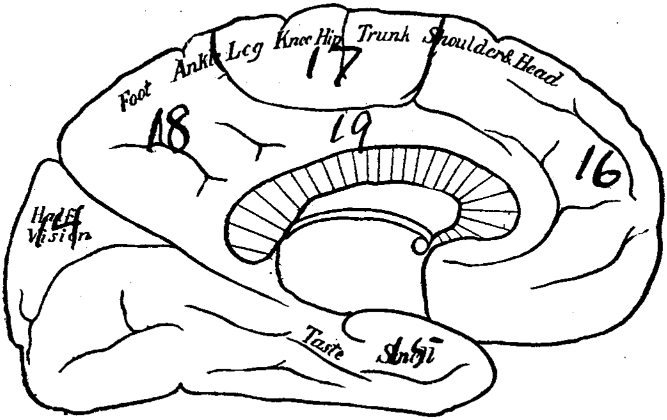


FIG. 7.

Figs. 6 and 7, showing the 19 sub-divisions of cortex for purposes of measuring thickness.

fashion. In order to see whether this method would throw any light upon the morphological characteristics of the present case, I made a series of one hundred and fifty measurements of the gray matter. These were made largely upon the cortex of the right hemisphere, but in the more important parts, viz., the central convolutions, the frontal and occipital lobes, examinations were also made of the left hemisphere. Measurements were made only of the convexity of the convolutions. I believe this to be the best practical way of making the examination. I have not found that the method described by Donaldson of measuring the cortex and the two sides of each convolution presents any great advantages. I took the brain after it had been hardened for three months in Müller's fluid so as to bring out the

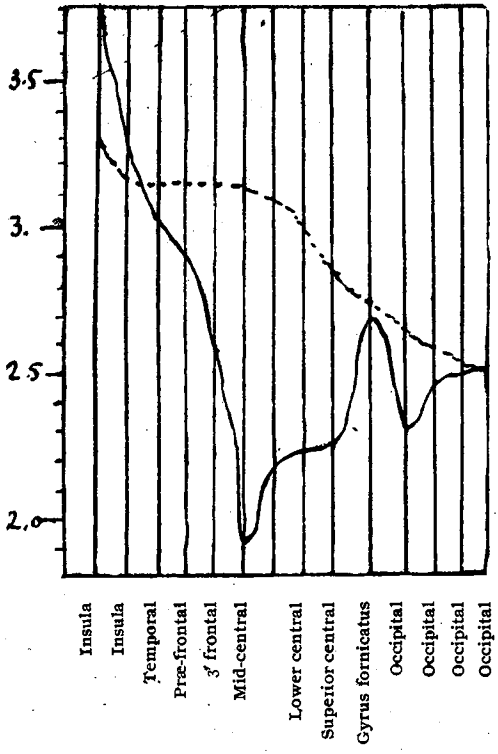


FIG. 8. Diagram showing the thickness of the cortex in the normal brain in hereditary chorea. Dotted line indicates normal curve, continuous line that of choreic brain.

coloring of the cortex well. I then divided it into nineteen different parts in the way shown on the diagram. (Figs. 6 and 7). With a Valentine knife sections were made from these different areas, they were measured and averages of the thickness of the convolutions for the different parts were computed. I then compared these with the measurements of normal brains as given by Donaldson, and prepared a table which shows the relations between the thickness of the cortex in my case and that of the normal brain. It will be seen (Fig. 8) that the line in my case runs a little below that of the normal for every part except the hippocampus and the occipital fissure, but that the relatively lowest part is in the præfrontal, the speech and the sensory motor centres. In what may be called the latent areas like the gyrus fornicatus, the temporal lobes and in the occipital lobes there is not very much falling away from the normal.

MEASUREMENTS OF THE THICKNESS OF THE CORTEX.

The following are the averages of 150 measurements, in millimeters:

Prae-frontal,	2.85 (20 measurements).
Third left frontal,	2.57 (left same as right).
Superior central,	2.2.
Parietal lobule,	2.2 (23 measurements).
Third central.	1.9 (9 measurements).
Lower central,	2.2 (9 measurements).
Hippocampus,	3.8 (15 measurements).
Gyrus fornicatus,	2.7.
Insula,	3.8.
Temporal,[1]	3.2 (13 measurements).
Temporal,[2]	3.1.
Occipital,	2.1 (14 measurements, left same as right).

MICROSCOPICAL EXAMINATION.

The microscopic examination of the brain was made by me without having previously read the article of Oppenheim; as I did not wish to study the sections with any preconceived ideas as to what I should expect. I examined sections of the central convolutions from both sides, also the parietal, occipital and frontal convolutions. The stains that were made with carminate of soda and then stained a short time with logwood gave the best pictures. I noted that in some sections very few changes could be seen. The membranes and the blood-vessels seemed to be fairly normal. I did not find abnormal changes in any part of the brain except in the central and to a less extent in the frontal convolution, the changes were most marked in the central convolutions. These showed a decided thinning of the gray matter, the pia mater was slightly thickened, but there was no meningitis strictly speaking. The tissue was in some sections very vascular and injected. The walls of the blood-vessels were slightly thickened, but not to any great extent. The perivascular spaces were not very much enlarged, nor were there any cells to be seen deposited around the walls of the blood-vessels. The nerve cells showed the most striking changes, especially those in the second and third layer, including the small and pyramidal cells. These cells did not stain with carmine very well. The first layer is much affected, being in places decidedly thin, so that the second and third cell layers are brought close to the periphery. The cells of the third and fourth layers are shrunken. The processes in many instances cannot be seen; the bodies look granula; their nucleus is enlarged. One in some cases sees small bits of pigment. In some of the areas that are most affected the small cells of the second and third layers have apparently been entirely destroyed, leaving small spaces and giving to the section a reticulated appearance. In the affected parts one may see small cells, probably scavenger cells, lying around the pyramidal cells. Nearly every one of the nerve cells in certain areas has from one to three of these small scavenger cells in the pericellular space fastened apparently upon the body of the nerve cell. This, perhaps, is chiefly marked in the third layer. The layer of the large pyramidal cells (fourth layer) is less affected, but some of these cells are nearly round in shape and have lost their processes and are evidently badly degenerated. The blood-vessels, as I have stated, in the affected areas are not very much changed, though the walls are somewhat thickened. Occasionally a high degree of vascularity of the parts occurs which may be due to the fact that the patient had had typhoid fever and in estimating the changes in the body of the cells and in the blood-vessels, I have taken this fact into consideration. These serious degenerative changes in the cells, however, are evidently of long standing and could not have been due to any febrile process, because they only occur in certain parts of the brain. A special examination was made of the third left frontal convolution, owing to the fact

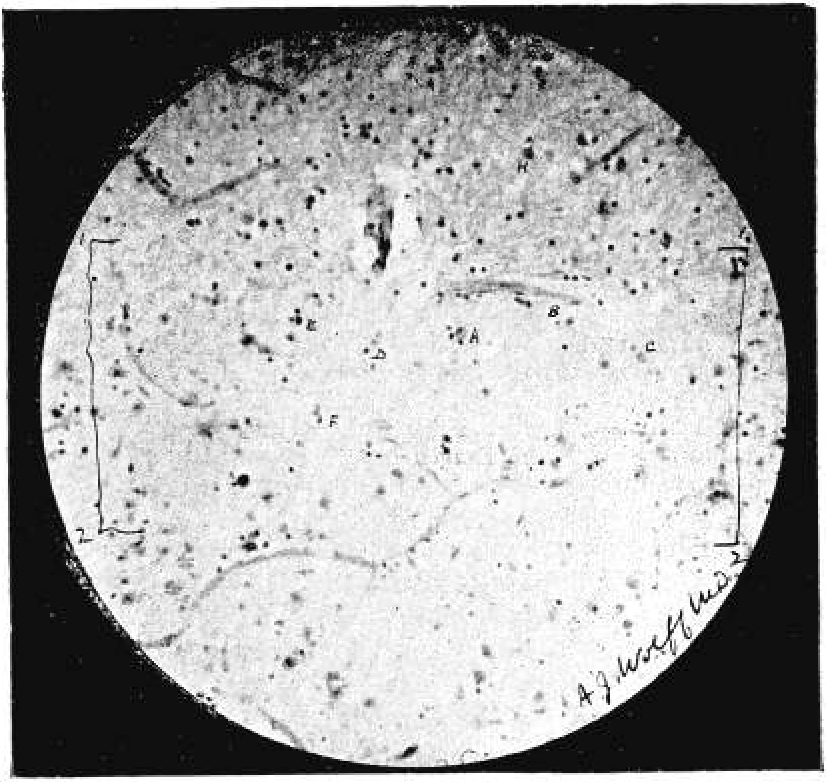


FIG. 9. Photograph of mid-central convolution ⅔ in. objective.

that the patient had disturbances of speech. But I could not discover any very characteristic change here. The sections of the occipital lobe showed no peculiar changes. The changes in the second, the middle and the upper part of the central convolutions were the most marked. Sections were made of the spinal cord at different levels, but there was absolutely nothing abnormal in this organ, unless it be that in the upper part there was a slight increase in the connective tissue forming the septa.

SUMMARY OF MICROSCOPICAL EXAMINATION.—Summing up now, the microscopic examination shows that the brunt of the process falls upon the central

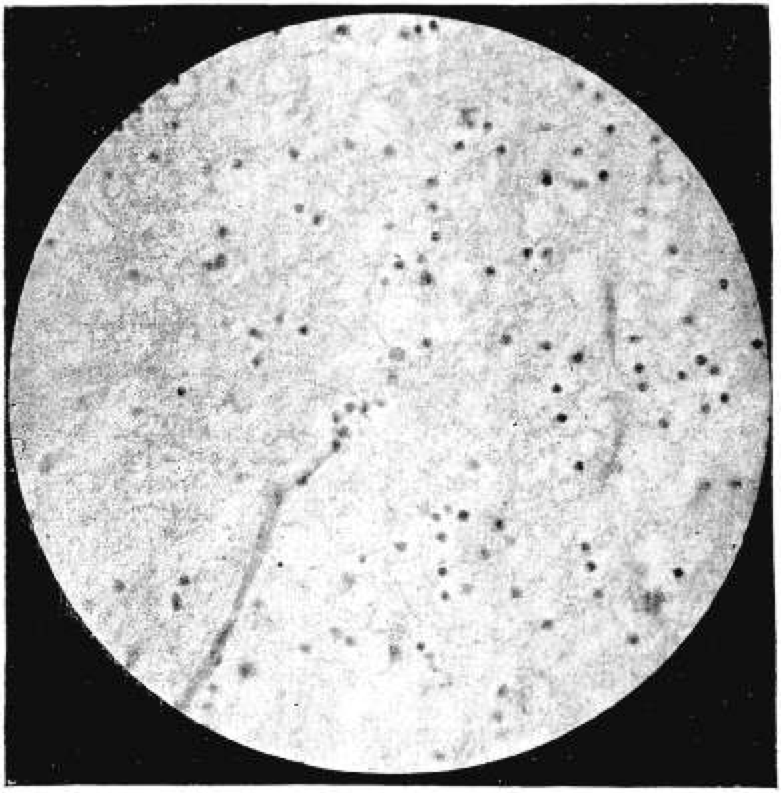


FIG. 10. Showing spaces left by atrophied cells. Same field as Fig. 9.

convolutions, that these are probably the first that begin to suffer, and that they suffer most intensely. It also shows that the process is not evenly distributed, but occurs in patches throughout the affected parts. This would explain, probably, the motor symptoms, the twitchings and choreic movements. This corresponds also with the observations of Oppenheim, that the process in hereditary chorea is a disseminated one. As to the intimate nature of the process I see no results to justify the opinion that it is in any sense an inflammation. There is in my sections no proliferation of connective tissue cells, and no exudation, no accumulation of leucocytes about the blood vessels, and only a slight amount about the nerve cells. The process in every respect corresponds to one of decay and degeneration; the nerve cell itself is the thing that first begins to die. In this respect hereditary chorea differs, I believe, absolutely from ordinary Sydenham chorea, where the process evidently begins in the blood, and is due to an irritant substance which is poured out from the blood upon the nerve cells in a way described by Sydenham himself. In Osler's work on chorea he concludes his study of the pathology of hereditary chorea with the statement that nothing has yet been found to explain the true nature of the disease. This statement is hardly true at the present time; to be sure, we may never get very much farther in the anatomical knowledge of disease, or if we do succeed in finding more recondite and distinctive changes in the cells, neuroglia and blood vessels, they will not help us to solve the mystery. But we have learned enough to see that the disease is one of decay and death, attacking the cortex of the brain primarily, and affecting one region after another until the part is so destroyed that dementia occurs and finally death ensues. From these facts I think we can, with the help of our knowledge of heredity and of the laws of pathology, deduce a fairly satisfactory explanation of the nature of hereditary chorea. I venture the opinion that the disease is itself a late development of a teratological defect. The patient is born with a brain which is abnormal. The cells originally bestowed upon him were cells that had only the capacity for living thirty or forty years instead of seventy or eighty. Just as cases of hereditary ataxia are born with defective vitality of sensory neurons in the spinal cord, so the cells of the motor cortex are in these people endowed with a short life, and after the strain of thirty years of work they begin to decay. There is no microbe, no poison, nothing in the environment of the individual or in his general physical make-up that produces this. It is simply a death at the age of thirty of cells which should and do in ordinary people live to the age of seventy. With this view of hereditary chorea as being simply a congenital defect, to be classed, perhaps, with idiocy and due to lack of development of the cortex, I believe we have an explanation of the disease which is reasonably satisfactory.

GENERAL SUMMARY.—Hereditary chorea, transmitted to the fifth generation through the female, death from typhoid fever in the fifth year of the disease. Peculiar anomalies of the brain, interrupted fissure of Rolando, absence of superior *pli de passage*, etc.; general thinning of the gray matter strikingly marked in the central convolutions; areas of great cell degeneration affecting most the angular and small pyramidal layer, the cell defect, primary, the vascular changes minor and secondary. The disease belongs to teratology. It is an innate defect in cell structure.

DISCUSSION.

Dr. MILLS, of Philadelphia.—Was any anæsthesia present in this case, or any form of sensory dicturbances.

Dr. DANA.—There was a condition of general hebetude.

Dr. MILLS.—This case is important in many respects, certainly most important in one. Dr. Dana expresses the true position not only of this case, but of a large number of cases which should be brought together in one class under a common designation, the basis of which designation would be the remark he made that these cases were teratological, and that they simply represented the fact that the individual was born with a certain potentiality of development, that at this age or that he was bound to be prematurely senile. This idea gives a broad basis for classifying certain diseases, such as hereditary chorea and other so-called family forms of disease.

SPECIMENS OF SPINAL CORD FROM A CASE OF HEREDITARY ATAXIA.

Dr. DANA.—In justice to Dr. Rook, of Quincy, Ills., I would like to pass around some sections of the cord that he sent to me, from a case of Friedreich's ataxia. The man had the disease about seven years, was of a family of four who suffered from this disease. He died of the disease, and this represents the terminal stage of it. I have two photographs which show not only the combined sclerosis which is characteristic of all cases, but some very interesting and peculiar perforations which ran through the whole cord and which I have never seen in any other cord. The holes are due to empty blood spaces, I think.

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